

Dr. Arrowsmith's Qualifications

- **1984 – 1986:** Epidemic Intelligence Service Officer at the National Centers for Disease Control
- **1986 – 1988:** Staff Epidemiologist in the Office of Epidemiology and Biostatistics at the FDA
- **1988 – 1990:** Deputy Director for Office of AIDS and Special Health Concerns
- **1990 – 1991:** Senior Medical Officer for HIV at the Agency for Healthcare Policy and Research
- **1991 – 1993:** Medical Review Officer in the Division of Antiviral Drug Products in the Center for Drug Evaluation and Research
- **1995 – 1996:** Medical Review Officer in the Division of Blood Applications, Office of Blood Research and Review in the FDA Center for Biologics Evaluation and Research
- **1986 – 1996:** Faculty at Georgetown Medical Center

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Opinions of Dr. Arrowsmith

- The Neurontin labeling was adequate under the regulations and provided appropriate information for safe and effective use
- The package insert, and the Investigator's Brochure prior to approval, included information concerning suicidal behavior and adverse effects on mood reported during clinical testing
- There was no reason for Pfizer to warn of suicidal behavior in the Neurontin labeling prior to the requirement of class labeling

21 CFR 201.57 (2002)

2002

§201.56

wide limits, depending upon the conditions being treated, it may not be possible in all cases to present an informative or useful statement of the recommended or usual dosage in the space available on the label or carton of the package. It is the view of the Food and Drug Administration that where such a situation prevails, compliance with this requirement would be met by a statement such as "See package insert for dosage information," where the detailed information is contained in such insert. However, if an informative, realistic, recommended or usual dosage can readily be set forth on the label, it should appear thereon.

§201.56 General requirements on content and format of labeling for human prescription drugs.

Prescription drug labeling described in §201.56(b) shall contain the information in the format required by §201.57 and shall meet the following general requirements:

(a) The labeling shall contain a summary of the essential scientific information needed for the safe and effective use of the drug.

(b) The labeling shall be true and accurate and neither prove in fact nor false or misleading in particular.

(c) The labeling shall be based on the best available data, derived from human experience, the results of clinical studies, or other data. If there is inadequate evidence of a lack of substantial net effectiveness, conclusions based on animal data, but necessary for effective use of the drug, shall be identified as such and with human data in the appropriate section of the labeling, based on which are listed in paragraph (d)(1).

(d)(1) The labeling shall contain the following information required under the following section and in the following order:

Description.
Clinical Pharmacology.
Indications and Usage.
Contraindications.
Warnings.
Precautions.
Adverse Reactions.
Drug Abuse and Dependence.

21 CFR Ch. I (4-1-01 Edition)

Overdosage.
Dosage and Administration.
How Supplied.
(2) The labeling may contain the following additional section headings, if appropriate and if in compliance with §201.57 (i) and (iii):
Animal Pharmacology and/or Animal Toxicology.
Clinical Studies.
References.

(b) The labeling may omit any section or subsection of the labeling format if clearly inapplicable.

(4) The labeling may contain a "Product Title" section preceding the "Description" section and containing only the information required by §201.56(a)(1), (ii), (iii), and (iv) and §201.56(b). The information required by §201.56(a)(1), (ii), (iii), and (iv) shall appear in the "Description" section of the labeling, whether or not it also appears in a "Product Title."

(c) The labeling shall contain the date of the most recent revision of the labeling, identified as such, placed prominently immediately after the last section of the labeling.

§201.57

adequate and well-controlled studies as defined in §314.126(b) of this chapter, unless the requirement is waived under §201.56 or §314.126(b) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions, or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in §314.126(b) of this chapter unless this requirement is waived under §201.56 or §314.126(b) of this chapter.

(d) Contraindications. Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it, use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it, or contin-

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ued use of the drug in the face of an acceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state "None known."

(e) Warnings. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be required to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug.

A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is a lack of substantial evidence of effectiveness for that disease or condition, and such use is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

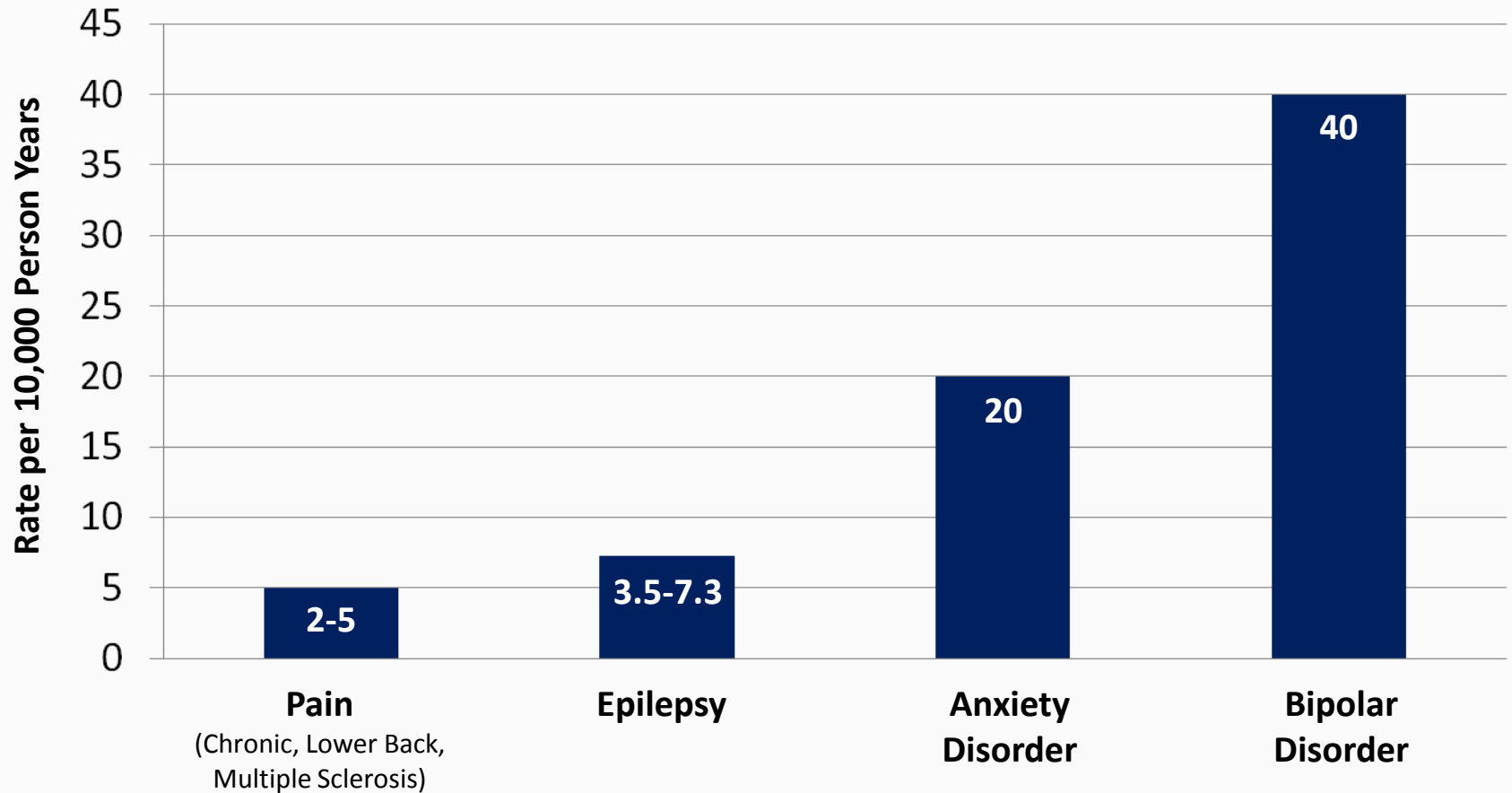
(f) Precautions. Under this section heading, the labeling shall contain the following subsections as appropriate for the drug:

(1) General. This subsection of the labeling shall contain information relevant to the drug to be exercised by the practitioner for safe and effective use of the drug, e.g., precautions not required under any other

The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.

Source: 21 CFR § 201.57, Pg. 22

Background Suicide Rates in Epilepsy, Pain, and Psychiatric Populations



Source: D.A. Fishbain, "Association of Chronic Pain on Suicide," 4 Seminars of Clinical Neuropsychiatry, 221 (1999); L. Nilsson, et al., "Risk Factors for Suicide in Epilepsy: A Case Control Study," 43 *Epilepsia* 644 (2002); A. Khan, et al., "Suicide Risk in Patients with Anxiety Disorders: A Meta-Analysis of the FDA Database," 68 *Journal of Affective Disorders* 183 (2002); L. Tondo, et al., "Suicidal Behavior in Bipolar Disorder: Risk and Prevention," 14 *Journal of Clinical Psychiatry* 1203 (2003).

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Randomized Controlled Trials (RCTs) And Uncontrolled Trials

- A randomized controlled trial (RCT) is a study in which subjects are allocated at random (by chance alone) to receive either the medicine under study or a control medicine, typically a placebo (sugar pill)
- In a double-blind RCT, neither the subject nor the physician knows which pill the subject is getting
- An uncontrolled study is one in which there is no comparison of the treatment medicine to a placebo

First Safety Update

TABLE 9. Summary of All Adverse Events in ≥1% of Gabapentin-Treated or Placebo-Treated Patients in Placebo-Controlled Add-On Therapy Studies, by Body System and Treatment Group (% of Patients)
(Page 3 of 4)

BODY SYSTEM Adverse Event	Placebo		Gabapentin (mg/day) ^a									
			600		900		1200		1800		Total	
	NDA N = 307	SU N = 378	NDA N = 53	SU N = 53	NDA N = 147	SU N = 147	NDA N = 231	SU N = 289	NDA N = 54	SU N = 54	NDA N = 485	SU N = 543
PSYCHOBIOLOGIC FUNCTION												
Nervousness	2.0	1.9	5.7	5.7	2.0	2.0	1.3	1.7	3.7	3.7	2.3	2.4
Depression	1.0	1.1	0.0	0.0	1.4	1.4	1.3	1.7	5.6	5.6	1.6	1.8
Thinking Abnormal	1.3	1.3	1.9	1.9	1.4	1.4	2.2	1.7	1.9	1.9	1.9	1.7
Emotional	0.7	1.3	0.0	0.0	0.7	0.7	0.0	1.4	1.9	1.9	0.6	1.1

Depression

Placebo

**SU
N = 378**

1.1

Gabapentin (mg/day)^a

**SU
N = 543**

1.8

There Is No Evidence of an Increased Risk Of Depression With Neurontin

May 29, 1992

Adverse Events

33

01

TABLE 9. Summary of All Adverse Events in ≥1% of Gabapentin-Treated or Placebo-Treated Patients in Placebo-Controlled Add-On Therapy Studies, by Body System and Treatment Group (% of Patients)
(Page 3 of 4)

BODY SYSTEM Adverse Event	Placebo		Gabapentin (mg/day) ^a								Total
	NCA N = 307	SA N = 53	600 N = 147	900 N = 221	1200 N = 54	1800 N = 495	2400 N = 543	3000 N = 543	3600 N = 543		
PSYCHOLOGICAL FUNCTION											
Depression	1.0	1.1	0.0	0.0	1.4	1.4	1.3	1.7	5.6	5.6	1.6
Thinking Abnormal	1.3	1.3	1.9	1.9	1.4	1.4	2.2	1.7	1.9	1.9	1.7
Emotionality	0.7	1.3	0.0	0.0	0.7	0.7	0.0	1.4	1.9	1.9	0.6
Anxiety	1.6	1.3	0.0	0.0	1.4	1.4	0.4	0.7	0.0	0.0	0.6
RESPIRATORY SYSTEM											
Rhinitis	2.9	2.7	7.5	7.5	0.0	0.0	4.8	3.8	12.0	12.0	4.5
Pharyngitis	1.3	1.6	3.8	3.8	1.4	1.4	2.5	3.1	3.7	3.7	2.9
Coughing	1.6	1.3	3.8	3.8	0.0	0.0	2.2	1.7	5.6	5.6	2.1
SKIN AND APPENDAGES											
Rash	1.3	1.6	3.8	3.8	0.7	0.7	0.4	1.4	1.9	1.9	1.0
Pruritus	0.7	0.5	1.9	1.9	2.7	2.7	0.9	0.7	0.0	0.0	1.4
Alopecia	0.0	0.0	1.9	1.9	0.0	0.0	2.8	2.1	0.0	0.0	1.4
Hair Loss	1.6	1.3	0.0	0.0	0.7	0.7	1.3	1.4	1.9	1.9	1.0
Hair Growth	1.6	1.6	0.0	0.0	0.0	0.0	0.4	0.3	1.9	1.9	0.4

^a Dosages of 600 and 1800 mg/day were used only in US studies, 900 mg/day was used only in non-US studies, and 1200 mg/day was used in both US and non-US studies.

01/01/2010/01/01/01/01

Adverse Event	Placebo 378 patients	Neurontin Total 543 patients
Depression	1.1%	1.8%

Not Statistically Significant

Source: First Safety Update, Pg. 33, Table 9

Rate of Psychobiologic Adverse Events Higher in Placebo

May 29, 1992 Epilepsy Trials

TABLE B. Summary of Body System Frequency for All Adverse Events in Placebo-Controlled Add-On Therapy Studies, by Treatment Group
(% of Patients)

Body System	Placebo		500		900		1200		Total
	N=303	N=308	N=53	N=53	N=147	N=147	N=733	N=789	N=485
Body as a Whole	10.5	10.9	11.5	11.5	18.4	18.4	27.7	27.3	26.5
Cardiovascular System	1.0	1.1	1.9	1.9	4.1	4.1	3.0	3.4	3.3
Digestive System	14.7	13.8	24.5	24.5	11.6	11.6	18.2	18.3	17.9
Immune and Lymphatic System	0.3	1.1	0.0	0.0	3.4	3.4	1.3	2.1	2.3
Musculoskeletal System	2.9	3.4	3.8	3.8	2.7	2.7	3.0	3.8	3.5
Nervous System	30.0	29.4	50.9	50.9	44.2	44.2	49.4	46.7	48.5
Psychobiologic Function	8.8	9.8	11.3	11.3	6.8	6.8	5.6	7.6	7.4
Respiratory System	6.5	6.3	17.0	17.0	3.4	3.4	11.3	9.7	10.7
Skin and Appendages	9.4	9.0	13.2	13.2	5.4	5.4	11.7	11.1	10.1
Urinary System	4.0	4.0	2.8	2.8	4.8	4.8	3.9	2.1	4.5
Special Senses	6.2	6.1	22.6	22.6	8.8	8.8	15.2	14.2	13.6
Laboratory Disturbances	3.3	3.8	3.8	3.8	9.5	9.5	4.0	11.1	6.8
Total Percent of Patients with an Adverse Event	56.7	55.6	86.8	86.8	68.0	68.0	71.3	73.7	76.1

^a Doses of 600 and 1800 mg/day were used only in US studies, 900 mg/day was used only in non-US studies, and 1200 mg/day was used in both US and non-US studies.

Body System	Placebo 378 patients	Neurontin Total 543 patients
Psychobiologic Function	9.0%	8.3%

Source: First Safety Update, Pg. 30, Table 8

Medical-Statistical Review Data Cutoff Over One Year Prior to Neurontin Approval

NDA #20-235 Medical-Statistical Review

74

8.0 Safety Findings

The purpose of this section is to assess the safety data submitted in this NDA in order to identify the risks associated with the use of Gabapentin administered in the manner suggested in the proposed labeling and to determine if any additional analysis may be needed to establish the reasonable safety of the drug system. This portion of the review will attempt to distinguish those adverse effects which may be attributed to the known pharmacokinetic actions of Gabapentin from any unexpected, local, or idiosyncratic effects. The safety review focuses on data derived from clinical trials sponsored by Parke Davis in support of this NDA. This section will contain the human safety findings, analyses and interpretations, coming from individual studies, pools of relevant studies, and the entire population exposed in the sponsor's development program.

8.1 Methods

In evaluating the safety of gabapentin the gabapentin-exposed population was examined for the most clinically serious adverse events and the most commonly collected and reported safety data were reviewed. The data that were relied upon for the assessment of serious adverse events were the summaries and case report forms of deaths, and dropouts due to adverse events as well as tabular summaries of adverse events determined to be serious by the investigators. In addition all case report forms that were provided in reference to these were reviewed. Finally a random check through other case report forms that were provided was made to screen for serious events that might have been missed through other methods, such as those that were not labelled as serious, but were considered serious by other criteria. The population relied upon for these was the total exposed population. Additional materials that were reviewed for this analysis included the Integrated Safety Summary (NDA Vol. 1.70-1.72 filed January 31, 1992), the Safety Update #1 (NDA Vol. 5.1-5.4 filed June 1, 1992), and Safety Update #2 (NDA Vol. 24.1-24.4) with the associated case report forms and tabular summaries of laboratory and adverse event data, the individual study reports of the major studies and the available CRFs as well as the extended treatment studies and the available case report forms provided for these studies.

This safety review is current as of 6/30/1992 in the drug's development except for deaths and serious adverse events which have been updated to 9/15/1992. The dates that are pertinent to this submission are shown below.

Data Cutoff Dates for Gabapentin Submissions

Document	Submitted	Safety Cutoff	Deaths Cutoff	Serious AE
NDA	1/31/92	4/30/90	8/31/91	6/30/91
First Safety Update	5/29/92	6/30/91	2/29/92	2/29/92
Second Safety Update	11/2/92	6/30/92	9/15/92	9/15/92

Relevant background information (noted in section 1.0) in the preclinical development of gabapentin necessitated a review of the safety data with the potential for carcinogenicity in mind. No other significant preclinical issues emerged during development, and indeed it appeared as though this drug was free of many of the adverse

This safety review is current as of 6/30/1992 in the drug's development except for deaths and serious adverse events which have been updated to 9/15/1992. The dates that are pertinent to this submission are shown below.

Dr. McCormick's Review Of Fourth Safety Update

December 28, 1993



The incidence of depression with suicidal ideation is reported in the 4th Safety Update as a severe adverse event, bringing the total to 10 cases reported. **There is a higher incidence of depression among epileptics with partial seizures as compared to the general population.**

One cannot determine based on the available data, largely uncontrolled, whether the reports here represent an increase in incidence or intensity of depression compared to that which is expected.

Source: Dr. McCormick's Review of Fourth Safety Update, 12/28/93, Ex. 7562

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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review and Evaluation of Clinical Data

NDA (supplement): 20-255 (Safety Update #4)
Review of the World Literature

Sponsor: Parke-Davis Pharmaceuticals

Brand Name (generic name): Neurontin (Gabapentin)

Indication: Refractory Partial Epilepsy

NDA Classification: 1 P

Original Receipt Date: December 15, 1993

Clinical Reviewer: Cynthia G. McCormick, M.D.

INTRODUCTION

This submission updates the safety profile as provided in the Integrated Summary of Safety provided in the original NDA along with the first three Safety Updates. Material that was reviewed for this analysis Ref. 140) which included the case serious adverse events.

This safety review is current as of deaths and serious adverse events that are pertinent to this submission.

Date Cutoff Date: 12/15/93

Document: Submitted NDA 1/31/92
First Safety Update 5/29/92
Second Safety Update 11/2/92
Third Safety Update 8/14/1993
Fourth Safety Update 12/15/93

There are no new data in Safety Update #4. The total number of patients 1993 was 5078 not including the protocols, Huntington's disease and for whom there were no case reports.

Depression: The incidence of depression with suicidal ideation is reported in the 4th Safety Update as a severe adverse event, bringing the total to 10 cases reported. There is a higher incidence of depression among epileptics with partial seizures as compared to the general population. One cannot determine based on the available data, largely uncontrolled, whether the reports here represent an increase in incidence or intensity of depression compared to that which is expected.

Status epilepticus: One additional case of status epilepticus has been reported in SUSA. This patient had a prior history of status epilepticus. The incidence of neurological serious adverse events has not changed significantly with the addition of new data.

Tumors: Since the last safety update there has been one report of a newly diagnosed breast cancer and a newly diagnosed cervical squamous metaplasia and intraepithelial neoplasia (CIN I-II). This brings the total of malignancies to 21. One of these occurred in a patient who received only placebo. These new reports do not alter the existing safety profile of gabapentin as previously reported.

Neurontin has been approved for marketing in the U.S. since 2/5/1993. There have been no post-marketing serious adverse events yet reported to the sponsor.

Summary of Drug Interactions:
No new drug-drug or drug-demographics interactions have been reported since the previous safety update.

Summary, Conclusions, and Recommendations:
There are no new data in the Safety Update #4 which alter the safety profile of this drug as presented in the initial NDA and Safety Updates #1, 2, and 3.

Review of the World Literature:
Review of the World Literature on Gabapentin, submitted in References 114 (September 17, 1993), 128 (October 30, 1993) and 138 (October 1993). There is no information in these sources which was not found in the NDA. Therefore this review do not alter the conclusions from the review of the NDA and Safety Updates 1-4.

Cynthia G. McCormick
Cynthia G. McCormick, M.D.
Clinical Reviewer
December 28, 1993

CC:NDA 20-255/NF-120/Katz/McCormick/Chamberlin
Mr. Nicks

The FDA Was Very Engaged During Review of the Neurontin NDA

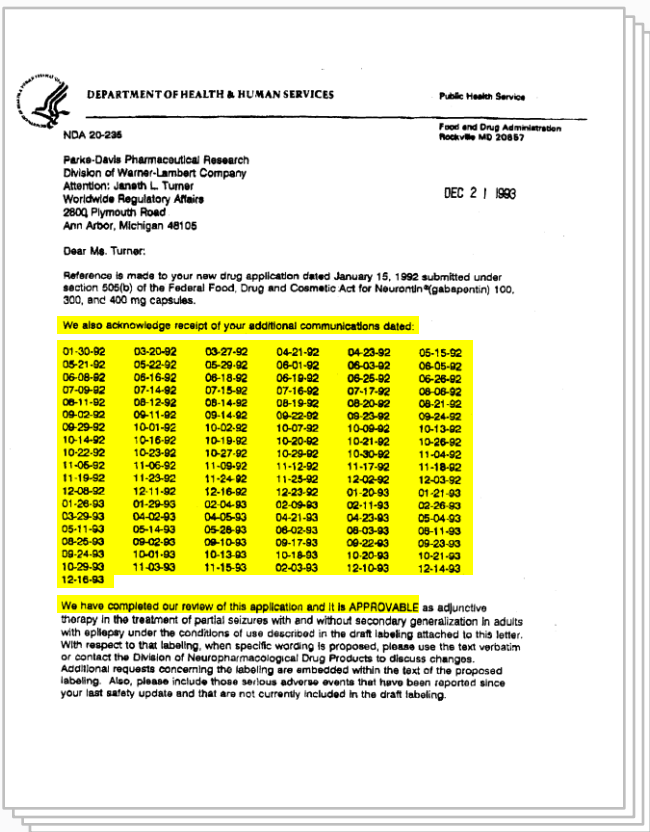
We also acknowledge receipt of your additional communications dated:

01-30-92	03-20-92	03-27-92	04-21-92	04-23-92	05-15-92
05-21-92	05-22-92	05-29-92	06-01-92	06-03-92	06-05-92
06-08-92	06-16-92	06-18-92	06-19-92	06-25-92	06-26-92
07-09-92	07-14-92	07-15-92	07-16-92	07-17-92	08-06-92
08-11-92	08-12-92	08-14-92	08-19-92	08-20-92	08-21-92
09-02-92	09-11-92	09-14-92	09-22-92	09-23-92	09-24-92
09-29-92	10-01-92	10-02-92	10-07-92	10-09-92	10-13-92
10-14-92	10-16-92	10-19-92	10-20-92	10-21-92	10-26-92
10-22-92	10-23-92	10-27-92	10-29-92	10-30-92	11-04-92
11-05-92	11-06-92	11-09-92	11-12-92	11-17-92	11-18-92
11-19-92	11-23-92	11-24-92	11-25-92	12-02-92	12-03-92
12-08-92	12-11-92	12-16-92	12-23-92	01-20-93	01-21-92
01-26-93	01-29-93	02-04-93	02-09-93	02-11-93	02-26-93
03-29-93	04-02-93	04-05-93	04-21-93	04-23-93	05-04-93
05-11-93	05-14-93	05-28-93	06-02-93	08-03-93	08-11-93
08-25-93	09-02-93	09-10-93	09-17-93	09-22-93	09-23-93
09-24-93	10-01-93	10-13-93	10-18-93	10-20-93	10-21-93
10-29-93	11-03-93	11-15-93	02-03-93	12-10-93	12-14-93
12-16-93					

We have completed our review of this application and it is

APPROVABLE

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Prior to Approval, FDA Carefully Reviewed Every Word of Neurontin Label

October 6, 1993

Park-Davis	
RECORD OF FDA CONTACT	
Date: October 6, 1993	Signature Name: Janeth L. Turner
Product Identification: (Add CI No. if known) Gabapentin CI-945	
NDA No: 20-235	IND No: 28,454
Initiated by: <input checked="" type="checkbox"/> P-D <input type="checkbox"/> FDA	Made: <input type="checkbox"/> In Person <input checked="" type="checkbox"/> Phone
FDA Contact Person:	
Name: Nancy Chamberlain	Title: CSO
Division: Neuropharmacology	Phone No. 1-301-443-3830
Purpose of Contact (Subject):	
Status of FDA review	
Summary:	
<p>Dr. Katz and Dr. Leber have decided to send the approvable package to Dr. Temple prior to negotiating labeling with us. The original version of the felbamate labeling had needed extensive revision, and attempting to work with the company to revise it prior to sending it to Dr. Temple had resulted in much confusion. They felt that the most recent revisions which we had submitted on September 3 were very good and developing an FDA version based on this, sending it to Dr. Temple as part of the approvable package, and then sending it to us to begin negotiations would be the most expeditious method.</p> <p>They have not yet sent the approvable package to Dr. Temple. There is nothing which FDA needs from us prior to sending the letter. The delay appears to be fine-tuning the labeling. They are reviewing every word, and since it has been so long since the Advisory Committee Meeting, sometimes they need to go back and refresh their memory as to what occurred.</p> <p>Nancy must have Dr. Katz' permission to tell me when it is sent to Dr. Temple. Nancy will follow up with Dr. Katz to determine if she can so inform me. Unless we instruct FDA otherwise, the approvable letter will be addressed to me. Nancy will call me when it is signed and send me a FAX of the letter once it is date stamped.</p>	

EXHIBIT
Turner 15
10-11-97

Confidential

WLC_JTurner_000717

They have not yet sent the approvable package to Dr. Temple. There is nothing which FDA needs from us prior to sending the letter. The delay appears to be fine-tuning the labeling. **They are reviewing every word**, and since it has been so long since the Advisory Committee Meeting, sometimes they need to go back and refresh their memory as to what occurred.

Source: October 6, 1993 Record of FDA Contact, WLC_JTurner_000717

FDA-Approved Label Told Physicians of Reported Suicidality Events, Regardless of Cause

December 30, 1993



Neurontin labeling draft 12/29/93

page 1

December 30, 1993

DESCRIPTION

Neurontin® (gabapentin capsules) is supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin. The inactive ingredients are lactose, corn starch, and talc. The 100-mg capsule shell contains gelatin and titanium dioxide. The 300-mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400-mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C Blue No. 2 and titanium dioxide.

Gabapentin is described as an empirical formula of $C_8H_{17}NO_2$



Gabapentin is a white to off-white powder, soluble in water and both basic and acidic solutions.

Neurontin labeling draft 12/29/93

page 28

intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, suicidal psychosis; **Rare:** choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, suicide gesture.

Respiratory System: Frequent: pneumonia; Infrequent: epistaxis, dyspnea, apnea; Rare: mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema.

Dermatological: Infrequent: alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex; Rare: herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling.

Urogenital System: Infrequent: hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, unable to climax, ejaculation abnormal; Rare: kidney pain, leukorrhea, pruritus genital.

[I]ntracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, **suicidal**, psychosis; **Rare:** choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, **suicide gesture**.

FDA-Approved Epilepsy Label Told Physicians About Reported Depression on Neurontin and Placebo

Table 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials (Events in at least 1% of Neurontin patients and numerically more frequent than in the placebo group)

TABLE 1. Treatment-Emergent Adverse Event Incidence in Controlled Add-On Trials (Events in at least 1% of Neurontin patients and numerically more frequent than in the placebo group)
(Page 1 of 2)

Body System/ Adverse Event	Neurontin ^a N = 543	Placebo ^b N = 378
Body As A Whole		
Fatigue	11.0	5.0
Weight Increase	2.9	1.8
Back Pain	1.8	0.5
Peripheral Edema	1.7	0.5
Cardiovascular		
Vasodilatation	1.1	0.3
Digestive System		
Dyspepsia	2.2	0.5
Mouth or Throat Dry	1.7	0.5
Constipation	1.5	0.8
Gastrointestinal Abnormalities	1.5	0.3
Increased Appetite	1.1	0.8
Hematologic and Lymphatic System		
Leukopenia	1.1	0.5
Musculoskeletal System		
Pain	2.0	1.9
Fracture	1.1	0.8
Nervous System		
Somnolence	19.3	8.7
Dizziness	17.1	6.9
Ataxia	12.5	5.6
Nystagmus	8.3	4.0
Tremor	6.8	3.2
Nervousness	2.4	1.9
Dysarthria	2.4	0.5
Amnesia	2.2	0.0
Depression	1.8	1.1
Thinking Abnormal	1.7	1.3

^a Plus background antiepileptic drug therapy
^b Amylase was often described as blurred vision

	Neurontin N=543	Placebo N=378
Depression	1.8%	1.1%

FDA Found a Numerically Higher Rate of Depression in Patients Given a Placebo Than Patients Treated With Neurontin in Pain Studies

Table 7.20 Percent of Treatment Emergent AEs in ≥3% of Patients, Neuropathy and Epilepsy Add-on Studies

	All Neuropathy GPN N=820	Neuropathy Placebo N=537	Epilepsy GPN N=543	Epilepsy Placebo N=378
Abdominal pain	1.0	1.3	1.9	
Abnormal ECG	0.3	1.3	0.6	
Acc. injury	1.9	2.3	2.2	3.3
Anti-seizure	1.2	2.1	0.4	0.3
AST/ALT	1.3	1.3	0.6	2.2
Subconjunctival	5.2	5.1	4.2	11.0
Ataxia	2.3	2.3	0.6	12.2
Back pain	2.4	1.3	1.7	1.9
Candidiasis	1.7	0.6	0.7	
Constipation	0.6	1.3	0.6	
Cystitis	0.3	1.3	1.1	0.9
Cytoplasmic	0.3	0.4	1.1	1.3
Depression	1.3	2.2	1.8	1.1
Dizziness	2.5	1.3	0.4	
Diarrhea	0.3	0.6	0.4	2.4
Disorder	2.3	2.3	1.1	4.3
Drug therapy	1.3	1.3	0.4	0.3
Dyspnea	1.1	1.2	0.6	
Edema	1.6	1.1	1.3	
Fatigue	2.5	1.2	1.0	
Headache	4.1	2.2	0.7	
Hyperkalemia	1.1	1.2	0.4	
Hyperthermia	0.3	1.3	0.6	
Hyperuricemia	0.4	0.3	0.6	1.1
Stomatitis	0.4	0.3	0.6	0.3
Increased creatinine	0.3	0.6	0.3	0.6
Malocclusion	1.6	1.1	1.1	0.6
Myalgia	0.3	0.6	0.4	0.3
Nausea	2.0	1.3	1.1	1.9
Nervousness	0.3	0.6	0.4	1.9
Oral pain	0.3	0.6	0.4	0.3
Pain	1.0	1.3	0.6	0.3
Pericarditis	0.3	0.6	0.4	0.3
Pharyngitis	0.3	0.6	0.4	0.3
Rash	0.3	0.6	0.4	0.3
Sinusitis	0.3	0.6	0.4	0.3
Sore throat	0.3	0.6	0.4	0.3
Tinnitus	0.3	0.6	0.4	0.3
Vaginitis	0.3	0.6	0.4	0.3
Weight gain	1.3	1.3	0.6	1.9

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NDA 21-397 doc

FDA Clinical Review: Treatment Emergent Adverse Events, Neuropathy and Epilepsy Add-on Studies

	All Neuropathy GPN N=820	Neuropathy Placebo N=537	Epilepsy GPN N=543	Epilepsy Placebo N=378
Depression	1.3%	2.2%	1.8%	1.1%
	Not Statistically Significant		Not Statistically Significant	

Source: May 24, 2002 FDA Clinical Review, Pg. 77, Table 7.20

FDA's 2005 'Minor' Change to Suicide-Related Adverse Event Terms in Neurontin's Labeling



November 22, 2005 E-Mail From FDA to Pfizer

-----Original Message-----

From: Calder, Courtney [mailto:CalderC@cdcr.fda.gov]
Sent: Tuesday, November 22, 2005 9:35 AM
To: 'Patel, Manini'
Cc: 'Evertsz, Mary Ann'; 'Phelan, Kevin (New York)'
Subject: RE: : Neurontin clarification by phone request

Hi Mary Ann,

Please proceed with the minor labeling changes pertaining to suicide-related events.

Thank you, Courtney

Courtney R. Calder, Pharm.D., LT USPHS
Regulatory Project Manager
Division of Neurology Products, HFD-120
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1050
Fax: (301) 796-9842
Email: calderc@cdcr.fda.gov

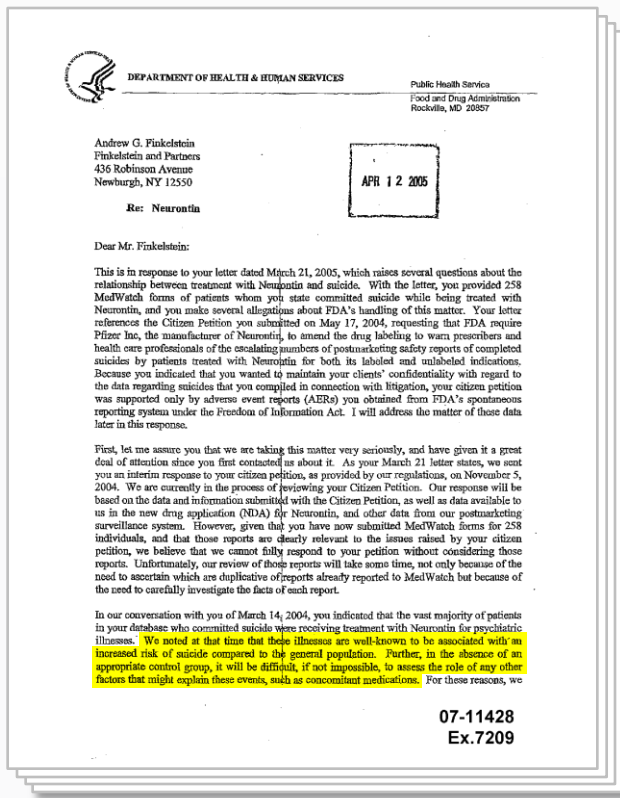
Please proceed with the **minor** labeling changes pertaining to suicide-related events.

Source: November 22, 2005 e-mail from Courtney Calder to Manini Patel (emphasis added)

FDA: Controlled Trials Are Only Way to Assess Whether Neurontin Is Associated With Increased Risk of Suicide

April 12, 2005 Letter From FDA to Plaintiff's Lawyers

We noted at that time that these illnesses are well-known to be associated with an increased risk of suicide compared to the general population. **Further, in the absence of an appropriate control group, it will be difficult, if not impossible, to assess the role of any other factors that might explain these events, such as concomitant medications.**



Source: April 12, 2005 Letter from FDA
to Andrew G. Finkelstein (emphasis added)

FDA: Controlled Clinical Trials Are the Only Way to Establish Whether AEDs Are Responsible for Suicide



From: CDER CDERS INFO [mailto:CDERSINFO@fda.hhs.gov]
Sent: Tuesday, April 01, 2008 8:28 AM
To: sprud@cosdrucor.com
Subject: Antiepileptic drugs

Dear Dr. Ruggieri:

Thank you for writing to the Food and Drug Administration (FDA). This is in response to your e-mail dated February 8, 2008, to Dr. Steven Galecki, regarding your scientific concern about the recent FDA alert announcing an increased risk of suicidal behavior and suicidal ideation in patients taking antiepileptic drugs. Your e-mail was forwarded to the Division of Drug Information (DDI) for a response.

In the near future, the FDA plans to hold an advisory committee meeting to discuss the current issues involving antiepileptic drugs. The primary purpose of the meeting will be to (1) make public the detailed results of the data analyses, (2) inform the committee of the actions we have taken and why, and (3) seek the committee's advice on whether our actions are appropriate and if any additional measures need to be taken. Our goal is to have the sponsors adopt the labeling changes for antiepileptic drugs by the time the meeting takes place, although we can not predict that this will be the case.

Portions of advisory committee meetings (depending on what is being discussed) are open to the public and oral presentations from the public are welcomed and encouraged. If you feel strongly about the class labeling change being implemented for antiepileptic drugs, I would suggest that you attend and/or present at the upcoming meeting.

If you are interested, please continue to visit <http://www.fda.gov/oc/advisory/default.htm> for information on when the meeting will take place. The Peripheral and Central Nervous System Drugs Advisory Committee will be at least one of the committees involved. The "notice of meeting" will provide the meeting location and instructions if you wish to present. In addition, transcripts and summary of minutes are usually available 30 days after the meeting and are also available from this site.

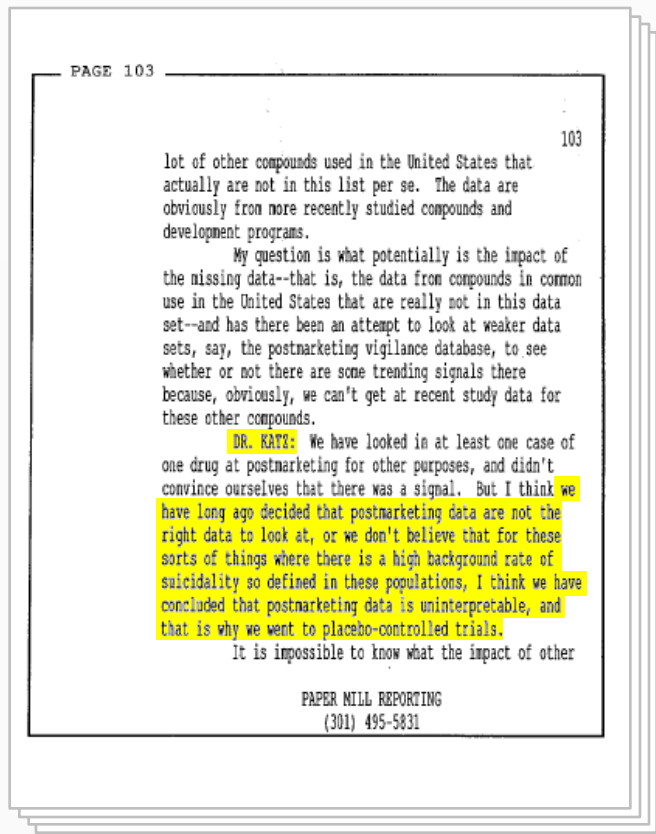
Concerning your question why data from the FDA Adverse Event Reporting System (AERS) has not been analyzed or made public, the agency does not believe that spontaneous post-marketing reports can be interpreted appropriately in this situation. Patients taking these drugs have a high background rate of suicidal thoughts/behaviors, and it is not possible to tell from AERS reports, whether the drug caused them. In the agency's view, the only way to

April 1, 2008 Letter From FDA

Concerning your question why data from the FDA Adverse Event Reporting System (AERS) has not been analyzed or made public, **the agency does not believe that spontaneous post-marketing reports can be interpreted appropriately in this situation.** Patients taking these drugs have a high background rate of suicidal thoughts/behaviors, and it is not possible to tell from AERS reports, whether the drug caused them. **In the agency's view, the only way to establish whether or not the drugs are responsible for suicidality is to analyze controlled trial data.**

Source: April 1, 2008 Letter from FDA to Dr. Alex Ruggieri (emphasis added)

FDA: Use Placebo-Controlled Trials Because Post-Marketing Data Are Uninterpretable

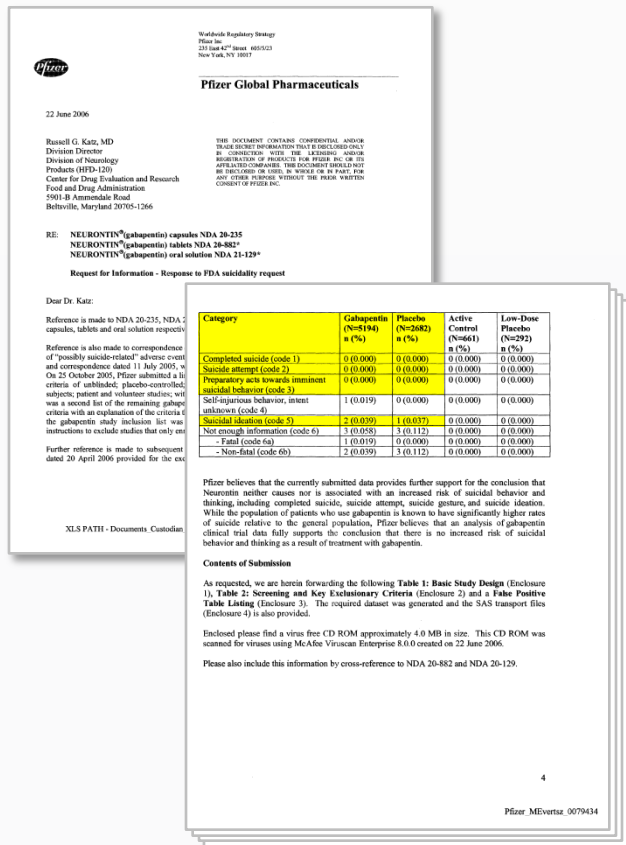


Dr. Katz: "...we have long ago decided that **post[-]marketing data are not the right data to look at,** or we don't believe that for these sorts of things where there is a high background rate of suicidality so defined in these populations, I think we have concluded that **post[-]marketing is uninterpretable,** and that is why we went to placebo-controlled trials."

Source: July 10, 2008 FDA Advisory Committee Meeting Transcript, Pg. 103

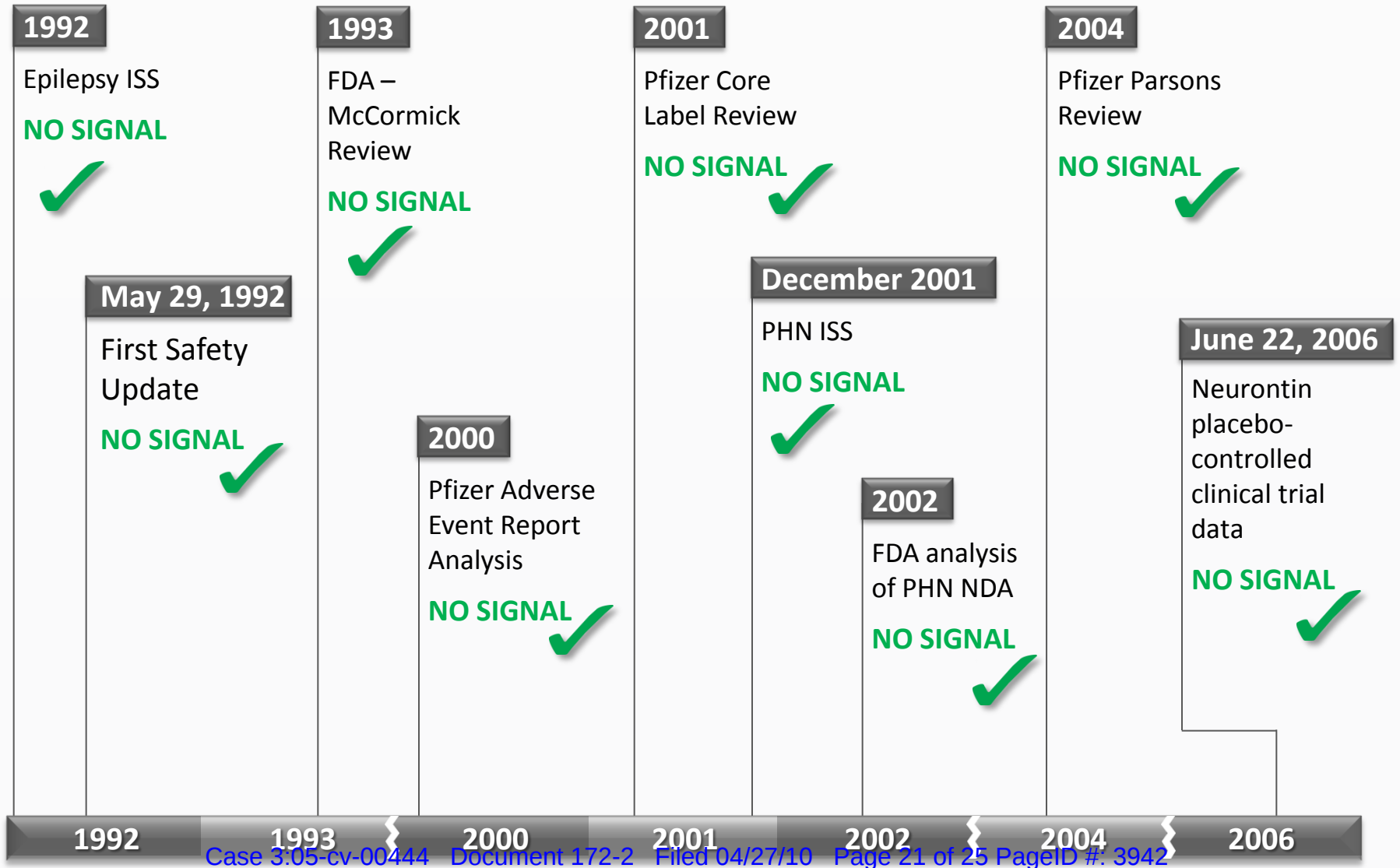
Controlled Trials: No Increased Risk of Suicide With Neurontin

June 22, 2006



Category	Neurontin: 5,194 patients	Placebo Control: 2,682 patients
Completed suicide	0	0
Suicide attempt	0	0
Preparatory acts towards imminent suicidal behavior	0	0
Suicidal ideation	2 (0.039) [2 out of 5,194 patients]	1 (0.037) [1 out of 2,682 patients]
Total	0.039%	0.037%

Evaluations of Depression and Suicidality



FDA Meta-Analysis – Entire Data Necessary to Draw Conclusions

DR. TWYMAN: I have a question for the statisticians. Let's assume that the effect is generalizable to the class of AEDs. But, if you look at the compounds individually, could one draw the conclusion individually that compounds have a risk, or **do you need the entire data set of all the AEDs put together in order to draw the conclusion that AEDs have a signal?**

DR. LEVENSON: I would say that we need the **entire data set in this case.**

Source: July 10, 2008 FDA Advisory Committee Meeting Transcript, Pp. 183-184

December 16, 2008 – FDA to Physicians: FDA Has Not Concluded AEDs Cause Suicidal Behaviors



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**Information for Healthcare Professionals
Suicidal Behavior and Ideation and Antiepileptic Drugs**

FDA ALERT [1/31/2008 Updated: 12/16/2008]: The FDA has completed its analysis of reports of suicidality (suicidal behavior or ideation (thoughts)) from placebo-controlled clinical trials of drugs used to treat epilepsy, psychiatric disorders, and other conditions. Based on the outcome of this review, FDA is requiring, under the authorities granted under the Food and Drug Administration Amendments Act (FDAAA) of 2007, that all manufacturers of drugs in this class include a Warning in their labeling and develop a Medication Guide to be provided to patients prescribed these drugs to inform them of the risks of suicidal thoughts or actions.

The drugs affected by these safety labeling changes are commonly referred to as antiepileptic or anticonvulsant drugs (see the list below). FDA's pooled analyses of 199 clinical trials of eleven antiepileptic drugs used as mono- and adjunctive therapies showed that patients who were randomized to receive one of the antiepileptic drugs had almost twice the risk of suicidal behavior or ideation (0.43%) compared to patients randomized to receive placebo (0.24%). This increase in the risk of suicidal thoughts or behavior represents the occurrence of approximately one additional case of suicidal thinking or behavior for every 530 patients treated with an antiepileptic drug.

The risk of suicidal thoughts or behavior was generally consistent among the eleven drugs analyzed and was observed in patients who were treated for epilepsy, psychiatric disorders, and other conditions. The relative risk for suicidal thoughts or behavior was higher in the clinical trials for epilepsy compared to trials for psychiatric or other conditions. However, the absolute risk differences were similar in the clinical trials for epilepsy and psychiatric indications. The increased risk was observed as early as one week after starting antiepileptic drug treatment and throughout the observed duration of treatment.

The increased risk of suicidal thoughts or behavior was generally consistent among the eleven drugs with varying mechanisms of action and across a range of indications. This observation suggests that the risk applies to all antiepileptic drugs used for any indication.

All patients who are currently taking or starting on any antiepileptic drug for any indication should be monitored for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression.

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA intends to update this document when additional information or analyses become available.

Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA intends to update this document when additional information or analyses become available.

Source: "Information for Healthcare Professionals: Suicidal Behavior and Ideation and Antiepileptic Drugs," December 16, 2008, Ex. 7558

Blume's 'Red Flags' Have No Credibility

Blume "Red Flag"	FDA Evaluated?	FDA Found Signal for Suicidality?
Dechallenge/ Rechallenge	YES	NO
Spontaneous Reports/PRR	YES	NO
Biologic Plausibility	YES	NO
1992 FDA Clinical Review	YES	NO
Clinical Trial Withdrawal	YES	NO
FDA Alert	YES	Yes (Class Label)

Opinions of Dr. Arrowsmith

- The Neurontin labeling was adequate under the regulations and provided appropriate information for safe and effective use
- The package insert, and the Investigator's Brochure prior to approval, included information concerning suicidal behavior and adverse effects on mood reported during clinical testing
- There was no reason for Pfizer to warn of suicidal behavior in the Neurontin labeling prior to the requirement of class labeling